ProMoT: Modular Modeling for Systems Biology

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Supplementary Data

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1 Handling of Modularity in Import and Export of Models

Import of models from formats which do not support modules into ProMoT's own modular format is not different to import into another format without modules. No automatic modularization (Saez-Rodriguez *et al.*, 2008) is performed during import.

All formats supported for export do not support modules. Modular models are flattened during export, an equivalent model representation containing all elements without modules or interfaces is created and this representation is then exported.

2 Model Validation and Optimization in Export

For export the model is translated into a "flat" representation. The equation set for the DAE system of the complete model is generated by aggregating all equations together with coupling equations for the interfaces. Validation of the model checks that the equation system is well-constrained using the Dulmage-Mendelsohn decomposition. When over- or under-constrained parts are detected the user is presented with this information and possible problem resolutions.

Optimization analyzes the algebraic part of the equation system, identifies explicit equations and sorts them according to their dependencies. Constant expressions and unnecessary variables are eliminated through symbolic transformations. Please refer for further information to Mangold *et al.* (2005) and Ginkel *et al.* (2003).

3 Model Documentation in ProMoT

ProMoT facilitates the generation of a model documentation in LaTeX or HTML. Whereas the export to LaTeX produces the documentation of a "flat" model, the HTML export conserves the modular structure of a model and maps it to an adequate hyperlink structure. This results in a convenient way to explore the modular model (e. g. modules, variables, equations) using a standard web browser (Figure 1).

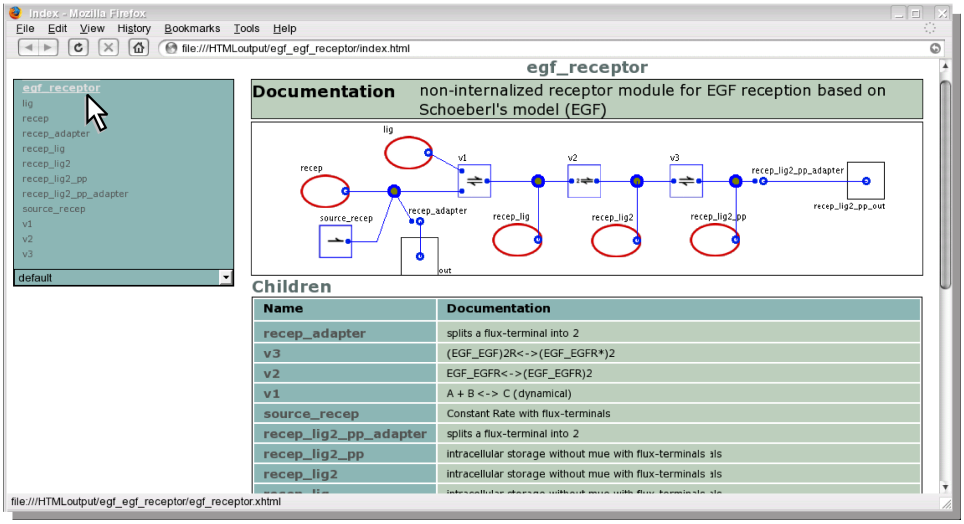

Figure 1: Model documentation exported in HTML format and viewed in a standard web browser.

4 Syntax checking validates the model in the background

The ProMoT Visual Editor integrates a syntax checking system which validates the model against structural modeling errors. This is particularly elaborated for the logical modeling formalism. The rules for the validation are based on requirements to the topological model-structure of logical models in the analysis tool CellNetAnalyzer combined with reasonable rules worked out together with experienced users of both tools.

The structural modeling errors are differentiated into several error types. In the ProMoT Visual Editor these types are visually emphasized by boxes. The different colors of the boxes encode the type of error:

- incomplete network-parts/missing connections (red boxes)
- wrong connections between library elements (white boxes)

- incorrectly used library elements (orange boxes)
- deprecated elements (turquoise boxes).

Furthermore, a detailed description of the error can be obtained in the tooltips of the elements.

For example when two logical gates are connected with each other, both are marked with white boxes by the checking system. The tooltip of each gate gives further detail to the error and advises to insert a compound between them (see Figure 2).

The syntax checking runs on-the-fly while the modeler is editing. Thus, errors can be eliminated shortly after they have been done and the time for localization and correction of structural errors prior to the model export can be significantly reduced.

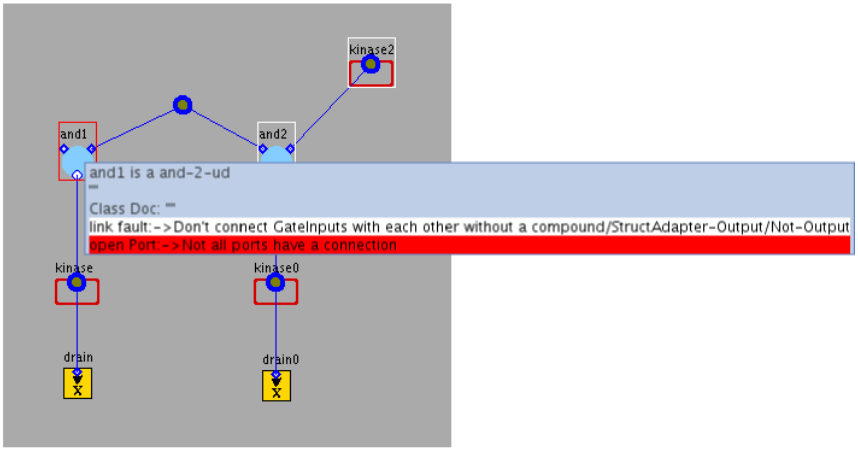

Figure 2: Syntax checking: an open port and a wrong connection of the element and1 are emphasized.

References

Saez-Rodriguez, J. et al., (2008) Automatic decomposition of kinetic models of signaling networks minimizing the retroactivity among modules., *Bioinformatics*, **24(16)**, 213-219.

Mangold, M. et al., (2005) Computer aided modeling of chemical and biological systems: Methods, Tools and Applications., *Industrial & Engineering Chemistry Research*, **44(8)**, 2579-2591.

Ginkel, M. et al., (2003) Modular modeling of cellular systems with ProMoT/Diva, *Bioinformatics*, **19(9)**, 1169-1176.